Summary of Safety and Probable Benefit

A. General Information

Device Generic Name: Transcatheter Cardiac Occlusion Device

Device Trade Name: AMPLATZER® PFO Occluder

HDE Submitter's Name and Address: AGA Medical Corporation
682 Mendelssohn Ave.
Golden Valley, MN 55427

Date of Humanitarian Use Device Designation: July 28, 2000

Date of Panel Recommendation: None

Humanitarian Device Exemption (HDE) Number: H000007

Date of Good Manufacturing Practices Inspection: October 2000

Date of Notice of Approval to the Applicant: April 5, 2002

B. Indications for Use

The AMPLATZER PFO Occluder is authorized by Federal (USA) law as a Humanitarian Use Device for use in the following indication only:

> The AMPLATZER PFO Occluder is intended for the non-surgical closure of a patent foramen ovale (PFO) in patients with recurrent cryptogenic stroke[1] due to presumed paradoxical embolism through a patent foramen ovale and who have failed conventional drug therapy[2].
>
> The effectiveness of this device in this indication has not been demonstrated.

C. Device Description

The AMPLATZER PFO Occluder is a percutaneous, transcatheter occlusion device. It is a self-expandable, double disc device made from a Nitinol wire mesh. The two discs are linked together by a short connecting waist allowing free motion of each disc. In order to increase its closing ability, the discs contain thin polyester fabric. The polyester fabric is securely sewn to each disc by a polyester thread.

[1] Cryptogenic stroke – a stroke occurring in the absence of potential phanerogenic cardiac, pulmonary, vascular or neurological sources.
[2] Conventional Drug Therapy – a therapeutic international normalized ratio (INR) on oral anticoagulants.

Table 1 Device Specifications

Order Number	RA Disc Diameter	LA Disc Diameter
9-PFO-025	25mm	18mm
9-PFO-035	35mm	25mm

The AMPLATZER® Delivery System includes:

- **Delivery Sheath** with Touhy-Borst Adapter - used to deliver the device.
- **Dilator** – used to ease penetration of tissue.
- **Loading Device** – used to introduce the AMPLATZER PFO Occluder into the delivery sheath.
- **Plastic Vise** – facilitates direction control and serves as the "handle" for disconnecting (unscrewing) the delivery cable from the device.
- **Delivery Cable** – the device is screwed onto the distal tip of the delivery cable, which allows for placement (and if necessary, retrieval) of the device.

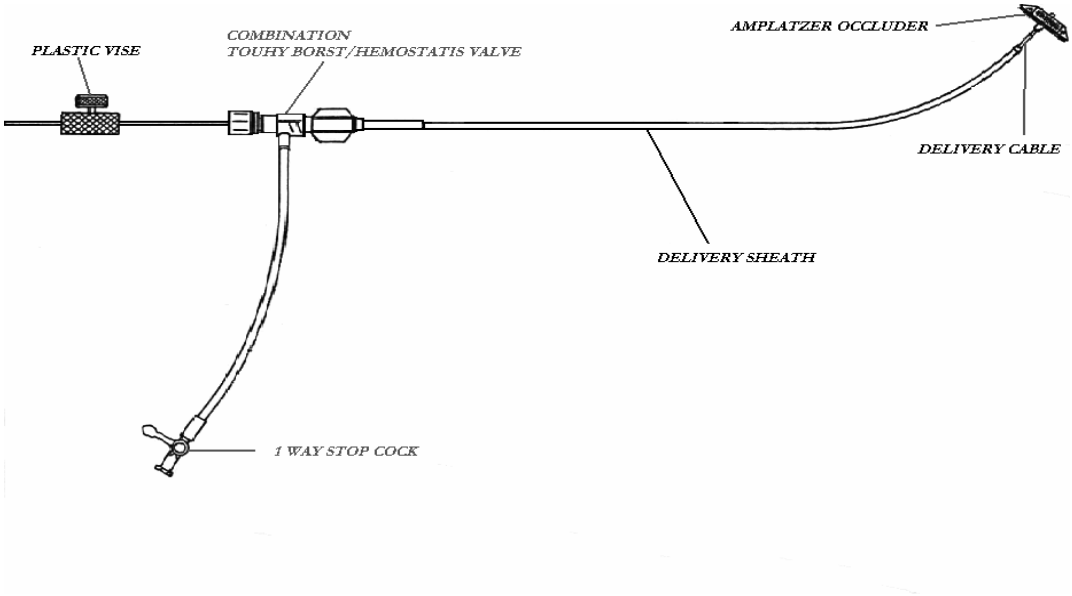


Figure 1 AMPLATZER PFO Occluder Device and Delivery System

- **Device Size Selection**

Transesophageal echocardiography (TEE) or similar imaging equipment (i.e., intracardiac echocardiography) is required to measure the distance of the defect to the free atrial wall, atrial septal size and distance to surrounding structures.

Using the distance of the rim of the defect to the free atrial wall, device selection is as follows:

Table 2 – Device Size Selection Criteria

If the distance from the PFO- to the free atrial wall is:	Select:
17.5 mm or greater	9-PFO-035
12.5 to 17.5	9-PFO-025
Less than 12.5 mm	Do not implant device

See Instructions for Use for device sizing method.

D. Contraindications

- Presence of thrombus at the intended site of implant, or documented evidence of venous thrombus in the vessels through which access to the defect is gained.
- Active endocarditis or other infections producing bacteremia.
- Patients whose vasculature, through which access to the defect is gained, is inadequate to accommodate the appropriate sheath size.
- Anatomy in which the AMPLATZER PFO device size required would interfere with other intracardiac or intravascular structures, such as valves or pulmonary veins.
- Patients with coagulation disorders who are unable to take antiplatelet or anticoagulant therapy.
- Patients with known hypercoagulable states.
- Patients with intra-cardiac mass or vegetation.

E. Warnings and Precautions

See Warnings and Precautions in the final labeling (Instructions for Use).

F. Adverse Events

Potential Adverse Events

Potential adverse events specific to device placement include, but are not limited to: device embolization, thrombus formation on the device surface with the risk of subsequent embolization, infectious endocarditis and device collapse due to structural failure.

Placement of the AMPLATZER PFO Occluder involves using standard interventional cardiac catheterization techniques. Adverse events commonly associated with these procedures include, but are not limited to:

Air embolus	Headache/Migraines
Allergic dye reaction	Hematoma and/or pseudoaneurysm
Anesthesia reactions	Including blood loss requiring transfusion
Apnea	Hypertension; hypotension
Arrhythmia	Infection including endocarditis
Brachial plexus injury	Perforation of vessel or myocardium
Death	Stroke-Transient Ischemic Attack
Fever	Valvular Regurgitation

Observed Adverse Events

Erosion of the free atrial wall was reported in two patients in international use. Eustachian valve entanglement in delivery system was reported in the literature (1). In the US Phase I study, the following adverse events were determined to be definitely, probably or possibly related to the device or the procedure. Fifteen (15) of the 57 patients who received a device reported 17 adverse events: cardiac arrhythmias (9), chest pain (2), neurologic symptoms (1), hematoma/AV fistula (2), groin pain (1), infection (1), allergic reaction (1).

G. Alternative Practices and Procedures

Alternative practices and procedures for patients with PFO's who have failed conventional drug therapy include surgical closure.

H. Marketing History

CE Mark was awarded on the device and delivery system in 1998. The devices have been marketed in the following countries:

Argentina	Guatemala	Singapore
Australia	Hong Kong	Spain
Austria	India	Slovak Republic
Belarus	Israel	South Africa
Belgium	Italy	Sweden
Brazil	Jordan	Switzerland
Canada	Kuwait	Turkey
Chile	Mexico	United Kingdom
China	New Zealand	Uruguay
Costa Rica	Norway	
Czech Republic	Pakistan	
Denmark	Portugal	
France	Russia	
Greece	Saudi Arabia	
Germany		

The AMPLATZER PFO Occluder and Delivery System have not been withdrawn from any market for reasons related to the safety and probable benefit of the device.

I. Summary of Preclinical Studies

1. Bench Testing

Bench testing was done to ensure that all initial design requirements were met. Testing was initially conducted on the AMPLATZER® Septal Occluder (reference IDE G960209 and PMA P00039). Material, processing and manufacturing methods of the AMPLATZER PFO Occluder device and the AMPLATZER Septal Occluder device are identical. Therefore, testing conducted on the AMPLATZER Septal Occluder was not duplicated on the AMPLATZER PFO Occluder. Table 3 summarizes testing completed on the AMPLATZER Septal Occluder.

In addition to the testing referenced in Table 4, withdrawal force to recapture the PFO Occluder device inside the sheath was evaluated. Four each of the 25 and 35 mm AMPLATZER PFO devices were tested in 8 and 9 French sheaths respectively. The force needed to recapture the Occluders did not exceed 5.6 pounds per square inch. With a safety factor of 4, the minimum pull test requirements for all parts and components of the AMPLATZER PFO Occluder was set at 22.2 pounds.

Table 3 Summary of Device Testing

Test	Samples		Specification	Results			
Pull Test Laser Weld – Marker Bands to Wire Braid	**Wire Dia.**	**N**	>22.2 lbs	**Wire Diameter**	**Mean ± SD (range) lbs**		
	.005	9		.005	36.79 ± 3.3 (32.9 – 44.7)		
	.006	11		.006	37.6 ± 3.8 (29.9 – 42.6)		
Pull Test Laser Weld - Screw Attachment to Marker Bands	**Wire Dia.**	**N**	>22.2 lbs	**Wire Diameter**	**Mean ± SD (range) lbs**		
	.005	7		.005	38.3 ± 5.8 (31.1 – 47)		
	.006	10		.006	47.9 ± 4.9 (34.95 – >50)		
Pull Test - Delivery Cable screw and device end screw	5		>22.2 lbs	**Mean ± SD (range) lbs** 26.4 ± 2.3 (23.4 – 29.15)			
Device Integrity	1		Structural Integrity must remain intact.	Structural integrity remained intact when single and multiple wires were cut, as well as when the left atrial disc post was cut.			
Life Cycle	240 ASD devices (30 each of the smallest & largest devices in each of the wire diameters) Only .005 and .006 wire diameters are reported here		Structural integrity must remain intact after 400 million cycles	Dev. Size	Wire dia.	# Fail	Description of findings
				11	.005”	0	
				17	.005”	2	1) 1 broken wire near end screw 2) 1 broken wire near marker band
				18	.006”	0	
				24	.006”	1	Broken wires in waist. Brass metal shaving found sandwiched between the two device discs during removal

Table 4 Summary of AMPLATZER Delivery System Testing

Test	Samples		Specification	Results	
Delivery Sheath Kink Resistance	**Size**	**N**	The sheath must not kink during normal clinical use.	**Size**	**Mean ± SD (range) degrees**
	8F	4		8F	112.5 ± 6.5 (105 – 120)
	9F	4		9F	112.5 ± 2.9 (110 – 115)
Pull Tests - Delivery Sheath Hub to Tubing	**Size**	**N**	Pull strength must not be <3lbs.	**Size**	**Mean ± SD (range) lbs**
	8F	4		8F	11.3 ± 0.1 (11.3 – 11.5)
	9F	4		9F	11.6 ± 0.1 (11.5 – 11.8)
Pull Test – Delivery Cable – Cable to Cable Screw Weld Joint	10		12 pounds	**Mean ± SD (range) lbs** 46.1 ± 5.5 (37 - >50)	
Pull Test – Sheath Marker Band	**Size**	**N**	Marker band must remain on catheter.	All samples passed.	
	8F	10			
	9F	10			

2. MRI Compatibility

AMPLATZER Occluders were tested to determine MRI Compatibility. No magnetic forces could be detected, and the device proved to be MRI compatible.

3. Corrosion Testing

a) Corrosion Testing – comparison evaluation between NiTi and 316SS

Further bench testing was conducted to compare the corrosion potential of Nitinol vs 316 Stainless Steel. Samples were prepared and formed per the recommendation of ASTM F746. The surface of the Nitinol sample was severed with a knife in order to address the issue of corrosion after destruction of the passive layer owing to abrasion.

The Nitinol sample did not display the general pitting found on the 316SS sample. In addition, there was no indication of crevice corrosion on the nickel-titanium sample as was seen on both the 316SS samples.

b) Corrosion – Bench Testing

Eight devices were tested for corrosion potential. The devices were degreased, rinsed with deionized water and blown with dry air. The electrolyte was prepared by dissolving 36.9g reagent grade sodium chloride in deionized water. After transfer to the corrosion cell, the electrolyte was deoxygenated by sparging with zero grade nitrogen for a minimum of 60 minutes.

The devices were suspended in the corrosion cell and maintained in the electrolyte at open circuit for 60 minutes before beginning the polarization scan (0.6 V/h). The electrochemistry was performed with a PAR 263 Potentiosatat.

In all devices the onset of corrosion occurred ca. 0.08 V from the open circuit potential. The corrosion potential (E_{CORR}) for the samples tested varied by ca. 0.08 V. The shape of the hysteresis curve indicates that localized corrosion may occur.

c) Corrosion – Animal Testing

Post mortem examination was conducted in an animal specimen wherein two devices were implanted (device #1 – implanted 18 months and device #2 implanted 14 months). Although the animal was implanted with the AMPLATZER Muscular Ventricular Septal Occluder, materials and methods are identical to the AMPLATZER PFO Occluder.

Analysis revealed both devices were nearly covered by neoendocardium. Gross inspection revealed no wire breakage. Light microscopy at 40x revealed a smooth surface. Scanning electron microscopy was carried out and compared to a new control wire. Both surfaces appear identical. No evidence of corrosion was observed for any of the devices. The wire surface appearance was typical of oxidized Nitinol wire.

Both devices were weighed (275 mg and 156 mg). If a corrosion of 10% would have been present which should have produced huge craters upon 3000 magnification, the daily dose of nickel would have been 15.4 micrograms per day which is 33 times less than the daily intake of nickel with a standard 2500 calorie diet.

d) Abrasion

A device was explanted from a swine after 3 months (at least 26 million cycles). A biopsy was taken from the neo-endocardium for histologic examination. The device was examined grossly, by light microscopy and by scanning electron microscopy (SEM). No broken wires were detected.

SEM examination was made at randomly selected wire intersection on both the large and small discs. The typical condition of the wires at the intersections was photographed. Results indicate that there are no signs of intersecting wires abrading each other.

4. Useful Life (Shelf Life/Sterilization)

Product and package stability testing of the AMPLATZER PFO Occluder and delivery system was performed. Visual inspection and physical testing indicated that the device performed within product specifications for up to three years. Based upon these results, an expiration date of 3 years has been established.

5. Biocompatibility Tests

The AMPLATZER PFO Occluder is constructed of Nitinol (a nickel-titanium alloy) and polyester. Sufficient information from the literature exists to

demonstrate biocompatibility of the material for use in an implantable device.[3,4,5] A chemical analysis was performed comparing the materials in the AMPLATZER Septal Occluder to a Nitinol vena cava filter and the polyester fabric used by surgeons to close cardiovascular defects. Results confirmed that the materials were virtually identical.

To further confirm the biocompatibility of the AMPLATZER PFO Occluder and the delivery system, the following tests were conducted in accordance with ISO 10993-1.

Table 5 Summary of Biocompatibility Tests

Test	***Result***		
	Nitinol Wire	***Polyester Fabric***	***Delivery System***
Cytotoxicity	Pass	Pass	Pass
Sensitization	Pass	Non-sensitizer	Non-sensitizer
Hemolysis	Pass	Non hemolytic	Non-hemolytic
Intracutaneous Injection (Irritation)	*Not required*	Pass	Pass
Toxicity	*Not required*	Pass (Subchronic)	Pass (Systemic)
Acute Systemic Injection	*Not required*	Pass	*Not required*
Ames Salmonella Mutagenicity	*Not required*	No mutagenic activity	*Not required*
Implantation	*Not required*	Moderate reaction	*Not required*
Chronic Toxicity	*Not required*	Pass	*Not required*

6. Animal Testing

Implantation of the AMPLATZER PFO Occluder device was utilized in animal studies to verify the feasibility and efficacy of the proposed concept. The objective of the study was to demonstrate that the PFO Occluder device was capable of providing rapid closure and endothelialization of patent foramen ovale. The intent of the study was to evaluate that safety and efficacy in animals with supportive study evidence to warrant a human clinical trial using the PFO device for correction of PFO defects. All placements in six animals were technically successful. One death resulted from ventricular fibrillation during placement. Pulmonary angiography and echo echocardiography showed complete occlusion of the PFO. Two animals were sacrificed after one month and four animals after three months. In the animals sacrificed at one month, histopathological examination showed partial endothelialization and in the 3-month follow-up group endothelialization was complete. This tissue in-growth demonstrated that the device was firmly fixed into position and was covered by a glistening non-thrombogenic layer of cells. In this final state, it was apparent that no thrombosis, shunting or dislodgment occurred. The device appears to be highly effective for

[3] Castleman LS, Motzkin SM, Alicandri FP, et al. Biocompatibility of Nitinol Alloy as an Implant Material. *J of Biomedical Materials Research* 1976; 10:695-731.
[4] Cragg AH, De Jong SC, Barnhardt WH, et al: Nitinol Intravascular Stent: Results of Preclinical Evaluation. *Radiology* 1993; 189-775.
[5] Prince MR, Salzman EW, Schoen, FJ, et al: Local Intravascular Effects of the Nitinol Blood Clot Filter. *Investigative Radiology* 1998; 23:294-300.

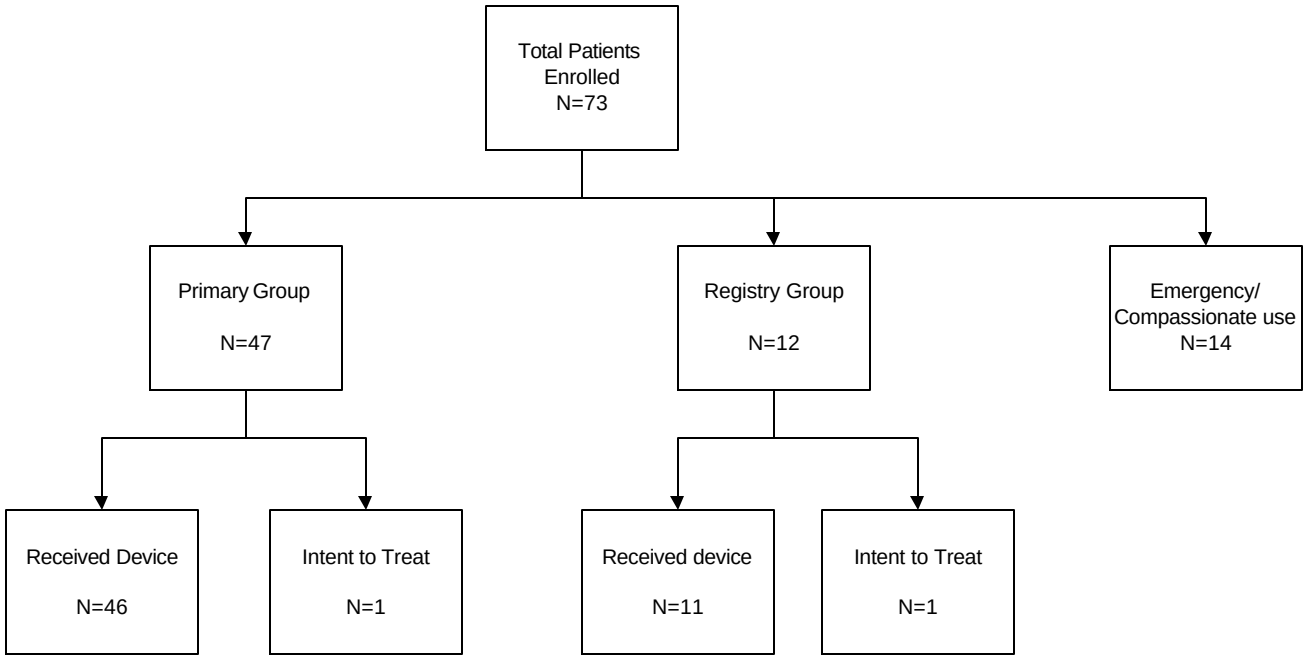
occlusion of PFO's. The introduction through a 7-9 Fr sheath allows placement as an outpatient procedure.

J. Clinical Experience:

1. US Clinical Study

AGA is currently conducting an Investigational Device Exemption (IDE) study to assess the safety and effectiveness of the AMPLATZER PFO Occluder in those patients with a patent foramen ovale (PFO) and history of cryptogenic stroke, TIA and/or peripheral embolization due to presumed paradoxical embolism. The study has a non-randomized pilot phase (Phase I) and a randomized phase (Phase II). Phase I involves 100 patients enrolled at a total of 7 centers.

As of November 15, 2001, there have been 73 patients enrolled in Phase I at 6 investigative sites. Patients were considered enrolled when they signed the informed consent.



a. Primary Group

Table 6. Baseline Demographics - Primary group

Variable		Results
Age (years)	Mean +/- s.d. (N) [range]	41.6+/- 11.2 (47) [14.7,59.1]
Gender		
Female		22/47 (46.8 %)
Male		25/47 (53.2 %)
Height (cm)	Mean +/- s.d. (N) [range]	171.7 +/- 13.0 (47) [130, 195]
Weight (kg)	Mean +/- s.d. (N) [range]	80.2 +/-20.3 (47) [45.0, 118.0]

Table 7 Procedural Information- Primary group

Variable		Results
Heart Catheterization Results:		
Right Atrium Mean	Mean +/- s.d. (N) [range]	6.0+/-3.0 (46) [0.0, 14.0]
Left Atrium Mean	Mean +/- s.d. (N) [range]	8.5 +/-3.8 (38) [2.0, 17.0]
Right Vent. Systolic	Mean +/- s.d. (N) [range]	23.0+/- 6.8 (46) [4.0, 40.0]
Pulm. Artery Systolic	Mean +/- s.d. (N) [range]	21.3+/- 6.9 (44) [7.0, 38.0]
Pulm. Art. Wedge	Mean +/- s.d. (N) [range]	8.9+/- 3.7 (44) [2.0, 17.0]
Size of PFO (mm)	Mean +/- s.d. (N) [range]	5.1+/- 3.8 (24) [1.0, 14.0]
Atrial Septal Aneurysm		15/42(35.7%)
Procedure Time (min.)	Mean +/- s.d. (N) [range]	86.1+/-42.1(43) [21.0, 240.0]
Fluoroscopy time (min.)	Mean +/- s.d. (N) [range]	17.4+/- 15.8 (43) [2.8, 92.0]
Device Size implanted:		
25 mm		22/46 (47.8%)
35 mm		24/46 (52.2%)
Residual Shunt [1]		
Grade 0 (no shunt)		26/46 (56.5 %)
Grade I (minimal shunt)		16/46 (34.8%)
Grade II (moderate shunt)		3/46 (6.5%)
Grade III (severe shunt)		1/46 (2.2%)

Counts may not add up to the number of total patients due to missing data.

[1]Shunt status is calculated based on the maximum amount of crossing bubbles at valsalva release via contrast enhanced echocardiography:

Grad 0- No bubbles Grad I- 1-5 bubbles
Grad II- 6-25 bubbles Grad III- >25 bubbles

Follow up

Twenty-four hours post procedure, a physical exam, EKG, chest X-ray and a 2-D Doppler echocardiogram with contrast at rest and during valsalva maneuver are performed.

Table 8. 24-Hour Follow up- Primary group

Variable	Results
EKG /Holter Monitor EKG Changes	 2/32(6.3%)
Chest X-ray results Device position changed	 0/44 (0.0%)
Residual Shunt Grade 0 (no shunt) Grade I (minimal shunt) Grade II (moderate shunt) Grade III (severe shunt) Testing not done	 30/44 (68.2 %) 9/44 (20.5 %) 1/44 (2.3 %) 2/44 (4.5 %) 2/44 (4.5%)

Counts may not add up to the number of total patients due to missing data.

[1]Shunt status is calculated based on the maximum amount of crossing bubbles at valsalva release via contrast enhanced echocardiography:

Grad 0- No bubbles Grad I- 1-5 bubbles
Grad II- 6-25 bubbles Grad III- >25 bubble

Table 9. 3-month Follow up-Primary group

Variable	Results
EKG /Holter Monitor EKG Changes	 0/26 (0.0 %)
Chest X-ray results Device position changed	 0/32 (0.0%)
Residual Shunt[1] Grade 0 (no shunt) Grade I (minimal shunt) Grade II (moderate shunt) Grade III (severe shunt)	 31/34 (91.2%) 3/34 (8.8%) 0/34 (0%) 0/34 (0%)
Closure Success[2]	31/34 (91.2%)

Counts may not add up to the number of total patients due to missing data.

[1]Shunt status is calculated based on the maximum amount of crossing bubbles at valsalva release via contrast enhanced echocardiography:

Grad 0- No bubbles Grad I- 1-5 bubbles
Grad II- 6-25 bubbles Grad III- >25 bubbles

[2]Closure Success is defined as number of patients where the PFO is closed (no bubbles)

b. Registry Group

The registry group consists of patients who have a documented PFO, but have failed conventional drug therapy.

Table 10. Baseline Demographics- Registry group

Variable		Results
Age (years)	Mean +/- s.d. (N) [range]	54.3 +/-19.2 (12) [11.3,81.5]
Gender		
Female		7/12(58.3 %)
Male		5/12(41.7 %)
Height (cm)	Mean +/- s.d. (N) [range]	173.8+/- 13.1 (12) [149.0,190.0]
Weight (kg)	Mean +/- s.d. (N) [range]	78.6+/- 14.3 (12) [47.9,107.0]

Table 11. Procedural Information- Registry group

Variable		Results
Heart Catheterization Results:		
Right Atrium Mean	Mean +/- s.d. (N) [range]	5.4+/-2.9 (12) [1.0,9.0]
Left Atrium Mean	Mean +/- s.d. (N) [range]	5.6+/-3.5 (9) [1.0,9.0]
Right Vent. Systolic	Mean +/- s.d. (N) [range]	24.2+/- 6.1 (12) [9.0,33.0]
Pulm. Artery Systolic	Mean +/- s.d. (N) [range]	21.9+/- 5.4 (12) [10.0,30.0]
Pulm. Art. Wedge	Mean +/- s.d. (N) [range]	8.6+/- 4.5 (11) [1.0,16.0]
Size of PFO (mm)	Mean +/- s.d. (N) [range]	5.1+/- 3.3 (9) [2.0,11.0]
Atrial Septal Aneurysm		3/11 (27.3%)
Procedure Time (min.)	Mean +/- s.d. (N) [range]	68.5+/- 22.0 (12) [43.0,114.0]
Fluoroscopy time (min.)	Mean +/- s.d. (N) [range]	16.2+/- 7.8 (12) [4.4,27.0]
Device Size implanted:		
25 mm		5/11 (45.5 %)
35 mm		6/11 (54.5 %)
Residual Shunt [2]		
Grade 0 (no shunt)		6 /11 (54.5%)
Grade I (minimal shunt)		4/11 (36.4%)
Grade II (moderate shunt)		0/11 (0.0%)
Grade III (severe shunt)		1/11 (9.1%)
Closure Success		6/11 (54.5%)

Counts may not add up to the number of total patients due to missing data.

[1]Shunt status is calculated based on the maximum amount of crossing bubbles at valsalva release via contrast enhanced echocardiography:

Grad 0- No bubbles Grad I- 1-5 bubbles

Grad II- 6-25 bubbles Grad III- >25 bubbles

Follow up

Twenty-four hours post procedure, a physical exam, an EKG, chest X-ray and a 2-D Doppler echocardiogram with contrast at rest and during valsalva maneuver are performed.

Table 12. 24-Hour Follow up- Registry group

Variable	Results
EKG /Holter Monitor EKG Changes	 3/9 (33.3%)
Chest X-ray results *Device position changed*	 0/11 (0.0%)
Residual Shunt[1] Grade 0 (no shunt) Grade I (minimal shunt) Grade II (moderate shunt) Grade III (severe shunt)	 7/11 (63.6%) 2/11 (18.2%) 0/11 (0.0%) 2/11 (18.2%)

Counts may not add up to the number of total patients due to missing data.
[1]Shunt status is calculated based on the maximum amount of crossing bubbles at valsalva release via contrast enhanced echocardiography:

Grad 0- No bubbles Grad I- 1-5 bubbles
Grad II- 6-25 bubbles Grad III- >25 bubbles

Table 13. 3-month Follow up-Registry group

Variable	N=3
EKG /Holter Monitor EKG Changes	 0/6 (100%)
Chest X-ray results Device position changed	 0/6 (100%)
Residual Shunt[1] Grade 0 (no shunt) Grade I (minimal shunt) Grade II (moderate shunt) Grade III (severe shunt)	 6/7 (85.7%) 1/7 (14.3%) 0 0
Closure Success[2]	6/7 (85.7%)
Stroke Patients[3] Modified Rankin Scale Score <3 Barthel Index Score <50%	 0/2 (0.0%) 0/2/(0.0%)

Counts may not add up to the number of total patients due to missing data.
[1]Shunt status is calculated based on the maximum amount of crossing bubbles at valsalva release via contrast enhanced echocardiography:

Grad 0- No bubbles Grad I- 1-5 bubbles
Grad II- 6-25 bubbles Grad III- >25 bubbles

[2]Closure Success is defined as number of patients where the PFO is closed (no bubbles)
[3]These indices were done only on patients who suffered stroke.

2. OUS Clinical Experience

The table on the following pages summarizes case histories that have been published, submitted for publication or presented at meetings.

Series	Purpose of Study	# of Patients (P)	Reported Complications Amplatzer PFO Occluder	Observations of study
Windecker, et al[6]	Investigate the long-term risk of recurrent thromboembolic events in patients with PFO and paradoxical embolism after percutaneous PFO closure	80 P attempted; 78 implanted with 5 different devices. **(4 Amplatzer PFO)**	1 device embolization	8 recurrent thromboembolic events (6 TIA's and 2 peripheral emboli) occurred in a mean f-up period of 1.6 ± 1.4 years (range, 0.1 to 5 years)
Windecker, et al[7]	Comparison study to investigate the safety & efficacy of the Amplatzer PFO Occluder.	**29 – Amplatzer (group 1**) 31 - Alternate PFO closure devices (group 2)	0 in group 1 (Amplatzer)	100% successful implant in all patients. Smaller sheath size and shorter fluoro times in group 1; Discharge residual shunt = 4 patients in group 1; 7 patients in group 2. No recurrent thromboembolic events were observed in either group.
Berger F, et al[8]	Report clinical use of the Amplatzer PFO Occluder	73 P; 23 with atrial septal aneurysm	None reported	Successful placement in all P. Mean PFO diameter: 9mm (4-20mm) mean fluoro time 7.5 min (0-23). Complete closure in all patients 12 weeks post procedure.
Berger, et al[9]	To determine if transcatheter closure of PFO prevent renewed cerebral embolic events	185 patients implanted with 5 different devices. **(139 Amplatzer PFO)**	1 report of unexplainable neurological symptoms (unknown which device)	Complete closure in 95.2% of P shown by TEE with contrast during Valsalva 3 months post.
Waight, et al[10]	Report on PFO closure in patients with orthodeoxia-platypnea	4 patients **(2 Amplatzer PFO)**	None reported	Average saturation increased from 81% to 96% with complete resolution of symptoms
Wahl, et al[11]	Assess long-term risk and risk factors for recurrent embolism after perc PFO closure	152 attempts with 6 different type devices (**45 Amplatzer PFO**)	0 procedural complication; 0 recurrent embolism 3 residual shunts	150 P received devices; 6 yr F-up (1.7 ±1.6 yrs; 258 P yrs) 1 recurrent stroke; 6 TIAs and 2 peripheral emboli

[6] Windecker S, Wahl A, Chatterjee T, et al: Percutaneous Closure of Patent Foramen Ovale in Patients with Paradoxical Embolism – Long-Term Risk of Recurrent Thromboembolic Events. *Circulation*, 2000;101:893-898

[7] Windecker S, Wahl A, Becker U, et al: Percutaneous closure of Patent Foramen Ovale in Patients with paradoxical Embolism using the Amplatzer PFO Occluder. *Submitted for publication*

[8] Berger F, Ewert P, Dahnert I, et al: Experience with the new amplatzer PFO occluder for occlusion of patent foramen ovale (PFO) after presumed paradoxical embolism. *Cardiol Young:* Vol 10, Supp 2; XXXV Annual General Meeting of the AEPC. P159.

[9] Berger F, Ewert P, Dahnert I, et al: Up to 8 years follow-up after interventional closure of patent foramen ovale (PFO) as a prevention of paradoxical embolism. *Cardiol Young:* Vol 10, Supp 2; XXXV Annual General Meeting of the AEPC. P134

[10] Waight DJ, Cao QL, and Hijazi AM: Closure of patent foramen ovale in patients with orthodeoxia-platypnea using the amplatzer devices. Catheter Cardiovasc Interv. 2000 Jun;50(2):195-8.

[11] Wahl A, Meier B, Haxel B, et al: Prognosis after percutaneous Closure of Patent Foramen Ovale in Patients with Paradoxic Embolism. *Neurology* 2001;57:1330-1332

Series	Purpose of Study	# of Patients (P)	Reported Complications Amplatzer PFO Occluder	Observations of study
Demkow, et al[12]	Report initial experience of Amplatzer PFO device in Poland.	3 P with at least one ischemic stroke episode	None	Complete closure confirmed at one month follow-up echocardiogram in each P. No repeat cerebral accidents reported.
Beitzke, et al[13]	Report experience with catheter closure of PFO using 4 different devices between June 1995 and June 2000.	162 P **(59 Amplatzer PFO)**	1 Arrhythmia	Implantations successful in all P. Serious catheter-related complications include 2 device embolizations and 2 venous bleedings. Residual leaks were reported in 5/116 patients with one receiving a second device for closure. Follow-up of 19.4 $\pm$ 16.2 months per patient, TIA and PRIND occurred in 3/116 P.
Sievert, et al[14]	Report experience with catheter closure of PFO using 7 different devices since August 1994.	281 P **(57 Amplatzer PFO)**	None	Implantations successful in all P. F-up of 1 – 71 months, recurrent embolic event occurred in 8 P (not with Amplatzer)
Beitzke, et al[15],	Report experience with catheter closure of PFO using 5 different devices between June 1995 and November 2000	202 P **(82 Amplatzer PFO)**	UNK	Early complications included 2 device embolizations, 5 retroperitoneal hematomas and 2 cardiac perforations; 8 late arrhythmias; 3 TIA following procedure. 175 patients followed for 3 to 62 months. 170 patients with 204 symptom-free patient years.
Krumsdorf U, et al[16]	Analyze morphological and functional characteristics of atrial septal aneurysm in PFO and ASD patients and to assess the feasibility and efficacy of 7 different devices between March 1997 and May 2000.	51 P **(5 Amplatzer PFO)**	None	Implantations successful in all patients. During follow-up, (0.6 – 37 months), a residual shunt was observed in 4 P 2 weeks after implantation and in 1P 6 months after implantation.

[12] Demkow M, Ruzytto W, Kwiecinski H, et al: Transcatheter closure of patent foramen ovale after cryptogenic stroke. Neur Neurochir Pol 2000 T.34(L), NR5 1005-1014
[13] Beitzke A, Schuchlenz H, Gamillscheg A, et al: Catheter closure of the persistent foramen Ovale: Mid-Term Results in 162 Patients. *J Interven Cardiol* 2001;14:223-230
[14] Sievert H, Horvath K, Zadan E, et al: Patent Foramen Ovale Closure in Patients with Transient Ischemia Attack/Stroke. *J Interven Cardiol* 2001;14:261-266.
[15] Beitzke A: PFO Closure: has its time come too? 3rd World Congress of Pediatric Cardiology, 2001. P834
[16] Krumsdorf U, Keppeler P, Horvath K, et al: Catheter Closure of Atrial Septal Defects and Patent Foramen Ovale in Patients with an Atrial Septal Aneurysm Using Different Devices. *J Interven Cardiol* 2001:14:49-55

Series	Purpose of Study	# of Patients (P)	Reported Complications Amplatzer PFO Occluder	Observations of study
Schwerzmann M, et al[17]	Compare the incidence of procedural complications and residual shunt between the Amplatzer PFO Occluder and another PFO device.	121 P **(66 Amplatzer PFO)**	There were more minor and major adverse events with the other PFO device than with the Amplatzer device (14.6% vs. 1.5%).	More attempts were required for placing the other device (9.1% vs 1.5%); larger sheath size required for the other device and significant residual shunt 6 months after closure persisted more frequently in the other device.
Spadoni I, et al[18]	Report experience of transcatheter PFO closure	39 P **(11 Amplatzer PFO)**	None	No recurrences of thromboembolic events in 30 P with paradoxical embolism.
Trepels T, et al[19]	Report first known case of penetration of an Amplatzer PFO occluder	71 P in series	One patient experienced pericardial tamponade	Surgery to remove the device revealed erosion of the right atrial roof and the aortic root.
Onorato E, et al[20]	Verify the role of ICE in transcatheter closure of PFO	103 P	None	No residual shunt and no recurrent symptoms 12 months post implant.
Anzola GP, et al[21]	Monitor the passage of microembolic signals in brain vessels	29 P	None	Complete occlusion in 28/29 P after 1 month. Severity of migraine dropped from a mean of 6 to a mean of 3 post closure.
Onorato E, et al[22]	Report combined use of ICE and TCD to quantify right to left shunts in real time.	31 P **(29 Amplatzer PFO)**	None	Mean fluoroscopy and procedural times were 9.45 $\pm$ 5 minutes and 57 $\pm$ 21 minutes, respectively.
Onorato E, et al[23]	Report on a patient with PFO with ASA and prominent Eustachian valve who underwent transcatheter closure	1	Prominent valve tissue was entrapped on the delivery cable and a piece of the EV was extracted unintentionally.	TTE 3 and 12 months post confirmed an ideally positioned device with no interference by the EV and no residual shunt.

[17] Schwerzmann M, Meier B, Wahl A, et al: Percutaneous closure of patent foramen ovale in patients with paradoxical embolism: Impact of PFO dedicated devices on procedural complications and residual shunt. *4th International Workshop Catheter Interventions in Congenital Heart Disease.* October 18-20, 2001, P536

[18] Spadoni I, Giusti S, Carminati M, et al: Indications and results of transcatheter closure of patent foramen ovale (PFO). *4th International Workshop Catheter Interventions in Congenital Heart Disease.* October 18-20, 2001, abstract

[19] Trepels T, Sievert H, Billinger K, et al: Amplatzer-PFO-occluder: Case report of a perforation. *4th International Workshop Catheter Interventions in Congenital Heart Disease.* October 18-20, 2001, abstract

[20] Onorato E, Pera I, Melzi G, et al: Intracardiac echocardiography: a novel approach to patent foramen ovale transcatheter closure. *4th International Workshop Catheter Interventions in Congenital Heart Disease*. October 18-20, 2001, abstract

[21] Anzola GP, Angeli S, Morandi E, et al: Transcranial doppler monitoring of right-to-left shunt during transcatheter closure of PFO: clues for migraine treatment? *4th International Workshop Catheter Interventions in Congenital Heart Disease*. October 18-20, 2001, abstract

[22] Onorato E, Pera I, Melzi G, et al: Intracardiac Echocardiography and transcranial doppler ultrasound to guide transcatheter closure of PFO. *4th International Workshop Catheter Interventions in Congenital Heart Disease*. October 18-20, 2001, abstract

[23] Onorato E, Pera I, Melzi G, et al: Large redundant eustachian valve interfering with Amplatzer PFO occluder placement: anatomo-clinical and technical implications. *4th International Workshop Catheter Interventions in Congenital Heart Disease*. October 18-20, 2001, abstract

Series	Purpose of Study	# of Patients (P)	Reported Complications Amplatzer PFO Occluder	Observations of study
Sievert, et al[24]	Report recurrent embolic TIA and stroke rate of patient implanted with closure devices	250 P **(44 Amplatzer PFO)**	Unknown	Annual event rate after PFO closure was 2.1%. Catheter closure of PFO reduces but does not eliminate the risk of cerebral events. During 235 patient-years, 5 P suffered from a recurrent embolic event (1 minor stroke, 4 TIA's). Unknown which device(s)
Butera, et al[25]	Report recurrent thromboembolic event rate using 4 different devices.	35 **(3 Amplatzer PFO)**	None	No residual shunt at 1 month follow-up. No patient experienced recurrence of a thromboembolic event.
La Rosee, et al[26]	Report results of one centers experience with different occlusion systems	102 **(UNK # Amplatzer PFO)**	Unknown	Successful placement in 99 of 102 patients. Occluder associated problems were: mild (41%) or extensive (11%) thrombus formation on the device; minor displacement (10%) or broken umbrella strut (6%). One patient experienced percardial tamponade which requried emergency surgical intervention. Complete occlusion was achieved in 71%. No case of cerebral emboli.
Pinto, et al[27]	Report on first three cases using the AMPLATZER PFO Occluder in Portugal	3	None	Procedure time ranged from 30-55 minutes and fluoro time 9-12 minutes. During the short follow-up all patients are asymptomatic and free of recurrent events.

[24] Sievert H, Horvath K, Zadan E, et al: Catheter Closure of PFO reduces but does not eliminate the risk of cerebral events: Acute and follow-up results in 250 patients. TCT Abstracts/ Poster, October 19, 2000; abstract number TCT-157.
[25] Butera G, Bini MR, Chessa M, et al: Transcatheter closure of patient foramen ovale in patients with cryptogenic stroke. *Ital Heart J* 2001 Feb;2(2): 119-20
[26] La Rosee K, Krause D, Becker M, et al: Transcatheter closure of atrial septal defects in adults. Practicality and safety of four different closure systems used in 102 patients. *Dtsch Med Wochenschr* 2001 Sep 21;126(38):1030-6
[27] Pinto FF, Sousa L, Abreu J, et al: Percutaneous occlusion of Patent Foramen Ovale in Patients with Paradoxical Embolism. *Rev Port Cardiol* 2001;20(7-8):747-757.

K. Conclusions Drawn from the Studies

The pre-clinical studies indicate that the AMPLATZER® PFO Occluder is biocompatible and has the appropriate physical and performance characteristics for its intended use, as stated in the labeling.

The clinical data generated from the Phase I US study indicates patients will not be exposed to an unreasonable or significant risk of illness or injury and that the probable benefit to health from the use of the device outweighs the risk of injury or illness, taking into account the probable risks and benefits of alternative forms of treatment.

The clinical data reported in the literature provide reasonable assurance of the safety and probable benefit of the AMPLATZER PFO Occluder when used in accordance with its labeling.

L. Panel Recommendations

The HDE was not taken to a meeting of the Circulatory System Devices Panel. However, a general Panel meeting was held on October 24, 1997, that included discussion of clinical trail requirements for this category of devices (i.e., occlusion devices) intended to treat congenital heart disease. Based a review of these recommendations and the data in the HDE, it was determined that a Panel meeting was not necessary for this device.

M. FDA Decision

CDRH has determined that, based on the data submitted in the HDE, that the AMPLATZER PFO Occluder will not expose patients to an unreasonable or significant risk or illness or injury, and the probable benefit to health from using the device outweighs the risks to illness or injury, and issued an approval order on April 5, 2002.

N. Approval Specifications

Directions for Use: See labeling.

Hazards to Health from Use of the Device: See INDICATIONS, CONTRAINDICATIONS, WARNINGS AND PRECAUTIONS, and ADVERSE EVENTS in the labeling.

Post-approval Requirements and Restrictions: See Approval Order.